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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT		ATTY. DOCKET NO.
08/712,302	09/11/96	GROTENDORST	G	07414/002003

EXAMINER		
18N2/0926		

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ART UNIT	PAPER NUMBER
1812	5

DATE MAILED: 09/26/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 6/23/97

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 17-28 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 22-27 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☒ Claim(s) 17-28 are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☒ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Compliance with Sequence Rules
☒ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

-SEE OFFICE ACTION ON THE FOLLOWING PAGES-

Part III: Detailed Office Action

Restriction Requirement:

Applicant's election of Group III, claims 22-27 in Paper No. 4, submitted 7/23/97 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, t).

Claims 17-21 and 28 stand withdrawn from prosecution as being drawn to a non-elected invention.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant must comply with the sequence rules, 37 CFR 1.821 - 1.825 within the time period set forth for response to this Office Action. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for response beyond the SIX MONTH statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Formal Matters:

The application is objected to because of alterations which have not been initialed and/or dated as is required by 37 CFR 1.52(c). A properly executed oath or declaration which complies with 37 CFR 1.67(a) and identifies the application by application number and filing date is required. The uninitialled alterations are in the form of underlining under the following words

"mitogenic" (page 2), "chemotactic"(page 2), "degenerate" (page 5 line 23) and "functionally unchanged" (page 5 line 27). See MPEP 605.04(b).

The disclosure is objected to because of the following informalities. Appropriate correction is required:

- The status of the related applications to which reference is made at page 1§1 of the specification should be updated.

Objections and Rejections under 35 U.S.C. §112:

Claims 22-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite for encompassing non-elected inventions, and should be amended to clearly indicate the elected invention, methods in which antibodies are used as the CTGF reactive agent.

Claim 22 is further indefinite for using the plural "diseases"; amendment to the singular would be remedial.

Claim 26 is further indefinite for depending from a non-elected claim.

Claims 22-25 and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for method of inhibiting cell proliferation using anti-CTGF antibodies, does not reasonably provide enablement for the scope of any possible CTGF reactive agent, nor for methods of treating undergrowth of cells using a CTGF reactive agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

With regard to the first point, while the specification clearly indicates that CTGF antibodies are envisioned, the claims read on the use of any agent which is "reactive" with CTGF. As the only such agent which is adequately described in the specification is an antibody, whereas the claims read on any CTGF reactive agent without regard to means, such that the claims read on proteins, chemical agents, etc., the Examiner concludes that the disclosure is not commensurate in scope with the claims.

With regard to claim 27, the specification clearly sets forth the use of anti-CTGF antibodies as antagonists of CTGF activity, for the inhibition of cell proliferation. Given this, the specification does not enable the use of such (or any other CTGF "reactive" agent) for the opposite purpose, that is, the stimulation of cell growth. It is not clear how, and it would require undue experimentation to determine such, the same group of agents can be used for two diametrically opposed purposes.

Rejections Over Prior Art:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 22-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pang (U.S.

Patent number 5,418,135) and Hart (U.S. Patent number 5,094,941) in view of Smith et al. (U.S. Patent number 5,147,294) and applicants admission in the specification that anti-PDGF antibodies are cross-reactive with CTGF, see page 7 line 15 and page 9, line 11.

Pang discloses that inhibition of PDGF activity is useful for inhibition or reversion of the formation of atherosclerotic plaques (see col. 2, beginning at line 45). At column 1, Pang discloses that excess cell proliferation is associated with the formation of such plaques, see lines 15-20, 33-35, and 49-51 for example. While Pang discloses the use of peptides for blocking binding of PDGF to its receptor (to inhibit such cell proliferation, e.g. see claim 1 and paragraph bridging columns 2-3) Pang does not disclose the use of anti-PDGF antibodies for such inhibition of cell proliferation.

Hart discloses monoclonal antibodies that are reactive with PDGF.

Smith et al. are cited as evidence that the use of antibodies as inhibitors of cytokines was well known in the art at the time the invention was made. See claim 8 of Smith et al., wherein an anti-nerve growth factor antibody is used as a nerve growth factor antagonist.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute an anti PDGF monoclonal antibody as taught by Hart in the method of Pang. The person of ordinary skill in the art would have been motivated to do so in view of the disclosure by Smith et al. that such antibodies are known in the art to be useful as antagonists, and would have had at least a reasonable expectation of success. It is noted that such a method would be expected to meet the limitations of the claims in view of applicants admission in the specification that anti-PDGF antibodies would be expected to be reactive with CTGF. Amendment of the claims to indicate that the antibodies used are specifically reactive with CTGF and not cross-reactive with PDGF would obviate this rejection.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Matsuoka et al. disclose the identification and purification of a PDGF-related protein of 34-36

kilodaltons (kD) from human wound fluid. The last paragraph of the first column, p. 4416 indicates that the peptides are biologically active as chemoattractants (e.g. chemotactic) and mitogens for connective tissue cells, and that they crossreact with anti-human PDGF IgG (antibodies).

Campochiaro et al. disclose the isolation of a PDGF-like protein from retinal pigment epithelial cells. Said protein has a relative mobility of 36-38 kD, is mitogenic and chemotactic, and binds to PDGF antibodies.

Shimokado et al. disclose the isolation of a PDGF-like protein of 37 kD, isolated from activated human alveolar and peritoneal macrophages. Said protein is mitogenic for connective tissue cells (p. 278), inhibited by anti-PDGF IgG (p.279) and competes for binding to PDGF receptors (paragraph bridging pages 279-280).

Ryseck et al. (Cell Growth & Differentiation 2:225) disclose cloning and expression of cDNA encoding fisp-12 from NIH 3T3 cells, a protein predicted to have 348 amino acids, with a predicted molecular weight of 37,792 daltons (p. 226, col. 2). The cDNA was in a biologically functional vector, and was used to transform *E. coli* (prokaryotic) cells, see page 226, second column for example. A comparison of the amino acid sequences of fisp-12 and CTGF reveals only 13 discrepancies in the region between residues 86 and 392 (based on the numbering of Seq. ID No: 1, see attachment which demonstrates the sequence alignment). There is greater divergence in the region preceding residue 86. However, Ryseck et al. identify this region as a signal sequence, which would have no effect on the activity of the protein. At the time of their disclosure, Ryseck et al. were unaware of the function of fisp-12, and made no mention of any ability to bind PDGF receptors.

Grotendorst et al., U.S. Patent number 5,408,040, to which the instant application claims priority, contains claims to antibodies which bind to CTGF but not to PDGF.

Advisory Information:

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 8:00 A.M. to 4:30 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Stephen Walsh, can be reached at (703)308-2957.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 305-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. **Please** advise the Examiner at the telephone number above when an informal fax is being transmitted.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to **[stephen.walsh@uspto.gov]**.

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Lorraine Spector

Lorraine Spector, Ph.D.
Patent Examiner

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